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The Costs to the U.S. Health Care System of Extending Marketing Exclusivity for Taxol[®]

Richard P. Rozek
Ruth Berkowitz

ABSTRACT. Paclitaxel is a chemotherapeutic agent used to treat ovarian, breast, and other cancers. It was discovered in part with U.S. taxpayer support. Bristol-Myers Squibb subsequently developed its brand of the product, Taxol[®]. In exchange for investing in Taxol, Bristol-Myers Squibb received five years of marketing exclusivity under the Waxman-Hatch Act. If it receives a two-year extension of its exclusivity beyond the current expiration date, December 27, 1997, consumers, insurers, and the government will incur significant costs. We estimate these costs in present value terms as:

- \$1.09 billion based on prices charged by sellers to intermediaries
- \$1.27 billion based on prices charged by intermediaries to final payers
- \$288 million for Medicare alone.

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INTRODUCTION

Paclitaxel is a cytotoxic chemotherapeutic agent used for ovarian, breast, and other cancers.¹ It was developed by the National Cancer Institute (NCI)

Richard P. Rozek, Ph.D., is Vice President and Ruth Berkowitz is Research Associate, both at National Economic Research Associates, Inc., 1255 23rd Street, NW, Washington, DC 20037.

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with U.S. taxpayer support. Paclitaxel, initially isolated from the bark of the Pacific yew tree, kills cancer cells in a manner unlike any other drug. For patients with metastatic cancers who have not responded to prior chemotherapeutic regimens, paclitaxel has provided a breakthrough, reducing tumors in 30% of cases (1).

In 1991, NCI and Bristol-Myers Squibb Company (BMS) signed a Cooperative Research and Development Agreement (CRADA). As a result of completing the product development under this agreement, BMS received exclusive rights to market Taxol, its brand of paclitaxel, for five years under provisions of the Drug Price Competition and Patent Term Restoration (Waxman-Hatch) Act. BMS negotiated the commercial pricing of Taxol with the National Institutes of Health (NIH). The price of Taxol is \$1,365/cycle at 175mg/m² once every 3 weeks. This price is higher than the cancer treatments Taxol supplanted (2). BMS agreed to provide Taxol at no cost to patients unable to pay for the drug and to NCI for additional clinical testing (3). Under the terms of the CRADA, BMS continues to conduct research on paclitaxel. So far, BMS has surpassed the \$114 million investment initially required by NIH and recently signed a new agreement estimated to represent up to \$30 million annually, or less than 4% of BMS's worldwide sales of Taxol in 1996, in payments, royalties, research support, and drug supplies to NCI (4).²

BMS earns substantial profits from a drug whose discovery costs were paid in part by U.S. taxpayers. In exchange for its contribution to the subsequent development of paclitaxel, BMS received five years of marketing exclusivity for Taxol; the exclusivity period expired on December 27, 1997. However, we understand there are attempts to extend BMS's marketing exclusivity for at least another two years.³ There are costs associated with extending exclusivity for Taxol for an additional two years. Consumers, insurers, and government agencies will pay higher prices for paclitaxel compared to the average price paid if competition from generic versions of paclitaxel emerges as soon as possible.

We developed a model to measure the added costs to the U.S. health care system of extending marketing exclusivity for Taxol. We will explain the facts and assumptions underlying our model, describe our calculations of the costs due to extending exclusivity for Taxol two years, and present our conclusions.

FACTS AND ASSUMPTIONS

BMS's Other Chemotherapeutic Products as a Guide

To estimate the additional health care costs of extending BMS's marketing exclusivity for Taxol two years beyond the original date of December 27,

1997, we analyzed sales and market share trends for the four innovative chemotherapeutic products initially marketed by BMS that are used to treat ovarian and/or breast cancer and that face generic competition. The four products (brands) are: etoposide (VePesid[®]), hydroxyurea (Hydrea[®]), megestrol acetate (Megace[®]), and mitomycin (Mutamycin[®]).⁴ Briefly,

- Etoposide is a chemotherapeutic agent indicated for testicular tumors and small cell lung cancer, with off-label uses for ovarian cancer and refractory advanced breast carcinoma as well as a number of other uses.⁵ VePesid is sold by BMS, and generic entry occurred in February 1994. Currently, there are two branded generic competitors and four other generic versions of etoposide available. Some of the generic versions are sold by more than one firm.
- Hydroxyurea is an antineoplastic agent indicated for recurrent, metastatic, or inoperable carcinoma of the ovary; melanoma; resistant chronic myelocytic leukemia; and primary squamous cell carcinomas of the head and neck.⁶ Hydrea is sold by BMS, and generic entry occurred in October 1995. To date, there is one generic version of hydroxyurea available.
- Megestrol acetate is an antineoplastic, progestational product available in both oral suspension and tablet form.⁷ Megestrol acetate tablets are indicated for the palliative treatment of advanced carcinoma of the breast or endometrium, although the product also exerts a direct cytotoxic effect on tumor cells. In addition, megestrol acetate is used off-label for the treatment of ovarian carcinoma.⁸ Megace is sold by BMS, and the first generic entry occurred in June 1988. Today, there are at least 3 generic product alternatives to Megace, which are sold by as many as 20 firms under different labels.
- Mitomycin is a chemotherapeutic agent indicated for treatment of disseminated adenocarcinoma of the stomach or pancreas in combination with other chemotherapeutic agents and as a palliative treatment when other modalities have failed. Off-label, mitomycin is used to treat breast, bladder, cervical, and esophageal carcinoma (6). Mutamycin is sold by BMS, and the first generic mitomycin entry occurred in June 1995. To date, there is one generic mitomycin product available.

Comparatively, paclitaxel is indicated "after failure of first-line or subsequent chemotherapy for the treatment of metastatic carcinoma of the ovary" and for "treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy" (6). Off-label uses for paclitaxel include treatment of lung cancer and acute lymphocytic and nonlymphocytic leukemia (6).

*Suppliers of Paclitaxel**Bristol-Myers Squibb*

We considered whether BMS would introduce its own unbranded or generic version of paclitaxel prior to other entry.⁹ In the past, BMS's subsidiary, Apotex, did not launch an equivalent for the other BMS oncology products. If BMS launches the first generic version of paclitaxel, the price of Taxol may not erode as much or as quickly and BMS's unbranded paclitaxel could capture a share of the generic sales.¹⁰ However, in this scenario, unit sales of Taxol would likely erode more than they would with other generic competitors, since physicians may readily accept BMS's unbranded paclitaxel in place of Taxol.¹¹ BMS's generic paclitaxel would capture a portion of the sales that would go to Taxol as well as a portion that would go to the other generic products. If BMS does enter with a generic paclitaxel product, it would sacrifice sales of Taxol to gain sales for its generic product. Since the economic effects of these two strategies tend to offset each other, we have assumed that revenues to BMS can be expected to remain more or less the same whether or not BMS launches its own unbranded product.

IVAX

IVAX has received tentative FDA approval of its New Drug Application for Paxene[®] (8).¹² However, due to BMS's orphan drug exclusivity status, IVAX's application may not be finally approved until 2004 (9). IVAX is pursuing options to overcome these regulatory hurdles. Therefore, IVAX may enter with its branded paclitaxel product within the next year.

Other Generic Competitors

Several other firms have expressed their intent to sell paclitaxel when BMS's exclusivity expires. Other than BMS and IVAX, Abbott Laboratories, Apotex, Biolyse Pharma, Biotechnology General Corp., Gensia, American Home Products Corporation, Mylan/Phytogen, Roxane Laboratories, Sabex, STC International, SuperGen Inc., XChem International, and Yew Tree Pharmaceuticals have announced plans to launch generic versions of paclitaxel (10). Cytoclonal Pharmaceuticals and ChiRex/InNova,¹³ in a joint venture, are potential entrants as well (11). These firms would likely create substantial price competition for BMS (13-18).

Price Erosion

The Average Wholesale Price (AWP)¹⁴ of Taxol is \$182.63 for 6mg/ml, 5ml (15). This price has neither increased nor decreased from year to year.

With generic competition, the average paclitaxel price will likely decrease each year (16). The extent of price erosion would depend on many factors, including the number of competitors and BMS's pricing strategy for its paclitaxel products. BMS may choose a zero or minimal price erosion strategy for Taxol to sustain its profit margin, or it may erode price quickly to maintain its market leadership. We assume BMS reduces the price of Taxol, since it is in a more price-sensitive market than products sold through retail pharmacies and the growing influence of managed care results in increased efforts to reduce costs.¹⁵ However, the price of Taxol will likely remain higher than the price of generic alternatives.

The number of firms producing paclitaxel and rate of market entry by generic firms affects brand and generic prices as well as brand market share erosion.¹⁶ If more firms enter quickly, lower prices and greater savings to consumers will likely result. Extending exclusivity for two years may affect the number of competitors as well as the date of market entry by generics. Marketing exclusivity precludes potential competitors from filing an Abbreviated New Drug Application (ANDA) with the FDA until exclusivity expires. Absent a legislative extension of exclusivity, firms may file ANDAs for paclitaxel beginning at the end of December 1997. If exclusivity is extended for two years, filings would not occur until at least December 1999. Even under the current exclusivity term, sales of generic paclitaxel are not expected to begin until October 1999. The terms of the Waxman-Hatch Act exclusivity and the time required for the FDA to approve ANDAs essentially provide BMS with additional time to market Taxol without any generic competition. With a formal two-year extension, sales of generic products would be delayed until October 2001, almost nine years from the first approval of Taxol for commercial sale. We base this view on data for the approval time of the first ANDA for blockbuster drugs, which was, on average, 22 months in 1996.¹⁷ In addition, approval for the first generic form of etoposide took 21 months, from July 1994 to March 1996 (Table 1).

Given the level of investment that production of paclitaxel requires due to the complex problems of locating a source of supply for the raw materials, some firms may decide not to produce a generic version of the drug if entry is delayed for two years. Delaying the opportunities to earn revenues by two years reduces the net present value of the expected profit from selling generic paclitaxel. Some or even most firms currently considering applying for an ANDA may not continue their development efforts if BMS receives additional exclusivity.¹⁸ However, we assume in our model that extending exclusivity does not discourage firms from applying for ANDAs to sell paclitaxel after December 1999.

For purposes of our model, we also assume that if IVAX does receive approval to market Paxene, it does not significantly affect the price or total

TABLE 1. First-Generic Blockbuster Prescription Drug Products Approved by the FDA Office of Generic Drugs.

Drug	Form	Strength/Dose	Company	Application Receipt Date	Approval Date	Elapsed Time (Years) (6)-(5) (7)	Indication	Notes
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Azathioprine	tablet	50 mg	Rosane	29-May-91	16-Feb-95	4.72	renal bone marrow transplantation and rheumatoid arthritis	
Cholestyramine	oral suspension	4 g/packet	Upsher-Smith	24-Apr-89	22-Feb-96	6.84	hypercholesterolemia	
Etoposide	injection	20 mg/mL/ 12.5 mL	Lederle	1-Jul-94	14-Mar-96	1.70	carcinoma	new strength
Clomipramine HCl	capsule	25, 50 & 75 mg	Geneva	1-Jun-93	28-Mar-96	2.82	obsessive-compulsive disorder	
Sucralfate	tablet	1 g	Biocryst	13-Nov-85	29-Mar-96	10.38	ulcer	
Estradiol	tablet	0.5, 1 & 2 mg	Watson	16-Sep-94	14-Mar-96	1.49	menopause	
Tiazofenone & Hydrochlorothiazide	capsule	37.5 mg/25 mg	Mylan	19-Jun-95	7-Jun-96	0.97	edema	
Clozapine	tablet	25 & 100 mg	Craigton	28-Sep-94	30-Aug-96	1.92	schizophrenia	
Nitroglycerin Transdermal Systems	-	0.2, 0.4 & 0.6 mg	Mylan	8-Nov-94	30-Aug-96	1.81	hypertension	
Sisegiline HCl	tablet	5 mg	Novopharm, Lederle & Endo	24-Sep-94	2-Aug-96	1.86	Parkinson's disease	
Clonazepam	tablet	0.5, 1 & 2 mg	Lammon	18-Nov-94	16-Sep-96	1.81	Gastrointestinal syndrome	
Glyburide	tablet	1.5 & 3 mg	Mylan	22-Nov-95	18-Dec-96	1.08	diabetes	
Procainamide HCl	tablet	1000 mg	Copley	1-Aug-94	13-Dec-96	2.37	ventricular arrhythmias	new strength
Median						1.86		

Source: "First Time Generic Approvals for 1996," Fax from Laura DeSimio, F-D-C Reports, to Ruth Berkowitz, January 17, 1997, Physician's Desk Reference: Generics, Medical Economics, 1996, and letter from George R. Scott, Chief, Drug Information Services Branch, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, to R. Berkowitz dated February 12, 1997, in response to FDA request for ANDA submission dates.

sales of paclitaxel. That is, until other firms receive approval, Paxene simply takes a portion of paclitaxel revenues from BMS, but does not provide significant savings to consumers.¹⁹ As mentioned above, IVAX has submitted an NDA for paclitaxel. Once approved, we assume that IVAX acts as a branded competitor if exclusivity is extended. It will be able to maintain a relatively high price for Paxene under BMS's umbrella. Three reasons for this assumption are: (1) IVAX is investing a large amount of resources in obtaining an NDA for its brand of paclitaxel compared to simply submitting an ANDA; it will price its branded product accordingly, (2) IVAX will also be granted protection from other competition in paclitaxel by extending exclusivity for BMS, sheltering it from price competition for at least a year, and (3) IVAX may be able to claim a safety benefit over Taxol since there are some differences in the clinical data between the two drugs (19). Therefore, we expect that entry by IVAX will not affect costs to the health care system.

Adding the Intermediary Markup

The costs to the health care system are revenues earned by sellers of paclitaxel to intermediaries with exclusivity extended to December 1999 minus revenues earned by sellers if exclusivity expires in December 1997. Our initial model relies on patterns of revenues for comparable drugs, excluding any markup added by intermediaries, such as hospital pharmacies or physician clinics. In general, the markup for generic drugs is higher in percentage terms than that for branded drugs (20). We initially calculate the costs of extending exclusivity in terms of total revenues to the sellers of paclitaxel to intermediaries. However, the costs to the payers for health care depend on the markup of the brand and generic products by the intermediaries. To estimate total costs to the health care system, we calculated the intermediary's margin assuming that all purchasers of branded and generic paclitaxel pay AWP.

Currently, BMS does not discount Taxol, so final purchasers generally pay AWP (21). To bring manufacturer sales of paclitaxel to the level of consumer spending, we used the margin between AWP and average BMS prices for our four comparable cancer drugs (Table 2).²⁰ We cannot determine if actual savings are better represented by our model with this margin.²¹ Nevertheless, the model with an intermediary margin gives us another estimate of the costs to the health care system of extending marketing exclusivity for Taxol.

Potential Therapeutic Competition

Paclitaxel is the first of a new class of cancer drugs with a unique mechanism of action that arrests growth of cancer cells by altering or interfering with microtubule function. It is a lifesaving drug. Paclitaxel is generally reimbursed by insurance companies for any use. Therefore, off-label sales are possible.²² Such chemotherapeutic products with unique characteristics are likely not to be price sensitive, and numbers of treatments should not increase nor decline significantly with changes in price.²³ A higher paclitaxel price will not result in substantial substitution with other chemotherapeutic agents or cancer treatments.

A possible therapeutic competitor for paclitaxel was introduced in mid-1996. It is a newly synthesized taxoid, Taxotere[®] (docetaxel). Since Taxol and Taxotere have subtle differences in their activity on tumors, Taxotere likely expands the taxoid market. However, the degree to which Taxotere sales will cannibalize sales of Taxol is not known. Additional competition at some point in the future is possible, as there are several chemotherapeutic drugs as well as other treatments for cancer in the research pipeline. However, a perfect substitute for Taxol other than from IVAX or a generic competi-

TABLE 2. Intermediary Markup on Branded and Generic Versions of Four Cancer Drugs.

Drug and Product	1991			1992			1993			1994			1995			1996		
	Manufacturer Price (\$)	Intermediary Price (\$)	Intermediary Margin (%)	Manufacturer Price (\$)	Intermediary Price (\$)	Intermediary Margin (%)	Manufacturer Price (\$)	Intermediary Price (\$)	Intermediary Margin (%)	Manufacturer Price (\$)	Intermediary Price (\$)	Intermediary Margin (%)	Manufacturer Price (\$)	Intermediary Price (\$)	Intermediary Margin (%)	Manufacturer Price (\$)	Intermediary Price (\$)	Intermediary Margin (%)
MEGESTROL ACETATE																		
(750 40 mg 100)																		
BMO (Mopson)	\$47.03	\$102.26	15.0%	\$83.03	\$106.61	12.0%	\$56.85	\$115.40	16.1%	\$100.00	\$119.00	15.0%	\$100.79	\$124.79	10.2%	\$57.01	\$129.78	25.3%
Pai Pharm	42.13	76.50	44.9%	43.03	78.50	42.6%	44.96	81.20	44.6%	49.37	93.35	47.1%	52.15	95.98	45.7%	42.17	123.29	69.6%
Bar	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gauco	52.81	81.75	35.4%	56.76	87.00	36.5%	52.86	87.00	39.5%	50.87	87.00	41.5%	57.11	106.00	46.1%	53.50	110.31	51.5%
Rugby	47.83	85.55	46.6%	58.30	89.55	34.7%	55.81	89.55	37.7%	52.77	89.55	41.1%	54.81	97.20	43.9%	57.50	106.00	45.8%
Schlen	61.67	88.25	5.5%	54.38	-	-	48.67	87.00	44.1%	48.88	96.00	49.1%	53.94	96.00	43.8%	48.40	106.00	51.0%
Quidwell	36.71	-	-	42.50	81.18	47.6%	41.35	81.18	49.1%	45.64	81.18	43.8%	50.83	89.55	43.2%	47.10	104.11	54.6%
Lemmon	-	-	-	45.00	-	-	43.92	74.00	41.1%	44.41	74.00	40.0%	54.42	98.00	45.0%	54.35	98.00	45.1%
MNS	35.78	-	-	32.68	-	-	35.83	-	-	33.18	-	-	36.00	-	-	36.67	-	-
Parmed	40.83	86.13	52.5%	48.19	85.86	43.9%	48.84	91.95	46.0%	52.67	97.85	46.2%	53.21	104.85	49.3%	42.95	104.85	59.0%
PL	36.85	-	-	46.72	-	-	48.36	-	-	52.38	-	-	47.84	-	-	47.93	-	-
Mayer	56.67	77.95	40.1%	41.95	78.75	46.7%	46.49	78.75	41.0%	80.00	87.40	31.6%	56.00	87.40	35.9%	48.00	87.40	45.1%
Mayer	-	-	-	38.13	102.88	62.9%	44.08	102.88	57.2%	43.50	102.88	53.6%	47.17	102.88	54.2%	53.00	102.88	58.4%
WCT	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bidon J.L.	40.59	85.49	52.5%	51.67	95.98	46.2%	63.65	92.48	-	120.00	92.48	-	75.00	-	-	62.98	-	-
Pharmaceutical Basic	-	67.43	-	-	-	-	37.06	-	-	-	-	-	-	-	-	-	-	-
Dann-Shane	30.00	79.00	62.5%	50.00	79.00	37.4%	-	79.00	-	75.00	-	-	46.25	-	-	60.00	-	-
Genelco	-	77.25	-	-	86.41	-	-	86.41	-	-	-	-	-	-	-	-	-	-
Algen	-	-	-	-	-	-	-	81.20	-	46.22	81.20	43.1%	41.51	95.99	56.8%	40.00	107.77	66.7%
Mason Dist.	-	-	-	-	-	-	-	64.83	-	40.00	64.83	38.3%	65.00	-	-	-	-	-
Genere Pharm	-	-	-	-	-	-	-	81.21	-	-	-	-	-	-	-	-	-	-
Bidone	40.61	81.75	50.3%	-	87.00	-	-	-	-	-	-	-	-	-	-	-	-	-
CLJA	42.86	-	-	33.33	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Best Genetics	43.33	70.32	38.4%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Simple Average: Generic	42.27	77.44	43.8%	45.78	86.46	44.3%	47.10	83.36	44.5%	54.48	86.80	43.4%	62.72	97.54	45.4%	48.33	103.86	53.6%
Generic as % of Branded Price	46.6%	0.76	-	48.3%	81.1%	-	48.6%	0.72	-	53.9%	72.3%	-	52.3%	78.2%	-	50.9%	80.0%	-
ETOPOSIDE																		
(100 20 mg/ml 5 ml)																		
BMO (Mopson)	95.47	117.06	18.4%	103.23	121.37	14.9%	108.77	131.49	18.8%	91.28	136.49	33.1%	89.07	136.49	40.4%	33.05	136.49	75.6%
USA 5943.01	-	-	-	-	-	-	-	-	-	79.65	131.45	38.4%	66.43	141.97	53.2%	36.46	141.97	72.5%
0291.01	-	-	-	-	-	-	-	-	-	-	-	-	40.15	-	-	29.43	140.00	78.0%
Pharmacia-Upjohn (Upjohn)	-	-	-	-	-	-	-	-	-	-	-	-	68.37	-	-	47.78	136.49	66.6%
BMO (Etoposide)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Simple Average: Generic	48.6%	0.76	-	48.3%	81.1%	-	48.6%	0.72	-	53.9%	72.3%	-	52.3%	78.2%	-	50.9%	80.0%	-
Generic as % of Branded Price	50.9%	0.65	-	48.3%	81.1%	-	48.6%	0.72	-	53.9%	72.3%	-	52.3%	78.2%	-	50.9%	80.0%	-

Drug and Product	1991			1992			1993			1994			1995			1996		
	Manufacturer Price	Intermediary Price	Margin (%)	Manufacturer Price	Intermediary Price	Margin (%)	Manufacturer Price	Intermediary Price	Margin (%)	Manufacturer Price	Intermediary Price	Margin (%)	Manufacturer Price	Intermediary Price	Margin (%)	Manufacturer Price	Intermediary Price	Margin (%)
HYDROXYUREA (CAPS 500 mg/100)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)
BMO (Hydra)	\$102.98	\$171.49	15.2%	\$109.90	\$125.96	12.8%	\$107.42	\$131.20	18.1%	\$110.16	\$131.20	16.0%	\$113.62	\$136.46	16.7%	\$111.26	\$141.93	21.6%
Rovane	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	85.02	127.73	33.0%
Generic as % of Branded Price	na	na	na	na	na	na	na	na	na	na	na	na	106.1%	na	na	76.9%	90.0%	na
MILCOMYCIN (VAL 30 mg)	202.53	366.21	17.9%	318.55	372.74	14.5%	327.73	403.80	18.8%	338.76	418.74	18.1%	333.13	425.49	23.3%	299.17	402.91	33.9%
BMO (Mammyph)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	289.00	434.80	35.0%
Chen	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	263.83	-	-
FDG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	275.45	-	-
CT	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	318.13	-	-
Single Average Generic	na	na	na	na	na	na	na	na	na	na	na	na	275.45	na	na	282.15	434.80	36.0%
Generic as % of Branded Price	na	na	na	na	na	na	na	na	na	na	na	na	82.7%	na	na	94.3%	96.0%	na
AVERAGE INTERMEDIARY MARGIN OF THE FOUR DRUGS	16.8%			13.8%			18.0%			21.0%			27.2%			38.1%		
BRANDED	43.8%			44.5%			44.5%			41.5%			45.8%			45.5%		
AVERAGE OF YEARS 1991-1996	22.6%			13.8%			18.0%			21.0%			27.2%			38.1%		
GENERIC	45.9%			44.5%			44.5%			41.5%			45.8%			45.5%		
Generic as % of Branded Price	73.1%			73.1%			73.1%			73.1%			73.1%			73.1%		
Average of Years 1991-1996	85.9%			85.9%			85.9%			85.9%			85.9%			85.9%		
All Manufacturer's Price	85.9%			85.9%			85.9%			85.9%			85.9%			85.9%		
All AMP Price	85.9%			85.9%			85.9%			85.9%			85.9%			85.9%		

Data either not available or the drug is not yet on the market.

Source: Data on revenues and units for marketed acetate, etoposide, hydroxyurea and mitomycin from January 1991 to December 1996. IMS America, IMS Corporation, received February 21, 1997, and Drug Topics, Redbook, Medical Economics, 1997-1998.

tor is highly unlikely. Usage of paclitaxel is likely to continue until 2005 and beyond.

Since the costs to the health care system from extending marketing exclusivity for Taxol will come in the first few years, therapeutic competition will not mitigate these costs. The prices of the brand and generic versions of paclitaxel may eventually converge and sales will decline. A breakthrough product that displaces paclitaxel is unlikely in the near term. Thus, distant potential therapeutic competition does not affect our estimate of costs to the health care system from extending exclusivity.

COSTS TO THE HEALTH CARE SYSTEM

Sellers' Prices

We constructed our model to calculate costs to the health care system over the period 1999 through 2005 if BMS succeeds in obtaining two additional years of exclusivity.²⁴ Since we expect market entry of the first alternative paclitaxel product to occur in early 1999, no losses occur in 1998.

We calculate costs by comparing spending on paclitaxel if exclusivity expires in 1997 with spending if exclusivity expires in 1999 (Scenario 1—exclusivity expires in 1997, and Scenario 2—exclusivity expires in 1999). We estimate brand, generic, and overall paclitaxel sales in both cases and subtract total sales in Scenario 1 from total sales in Scenario 2. Sales in this case are sales by the manufacturer or distributor of the product. These sales are to organizations such as wholesalers, hospitals, or physician clinics—not to the final consumer.

We used analysts' reports and the trend in sales of BMS's other innovative breast and ovarian cancer drugs that are subject to generic competition and applied that trend to estimate future Taxol revenues as follows:

- We assume that 1996 Taxol revenues in the U.S. are \$590 million, as estimated by Alex. Brown in November 1996 (23). In addition, we assume 1997 Taxol revenues to be \$700 million, as estimated by Lehman Brothers in January 1996²⁵ (24).
- The trend in the data for the 4 cancer drugs revealed that branded revenues increase at an average of 12.4% from the 2 years before generic entry to the year before entry. We applied this rate of increase to Taxol from 1997 to 1998 in both scenarios. In both scenarios, generic entry does not occur in either of those years; therefore, the rate of revenue growth should be equal.
- In addition, we observed, on average, a 4.0% average revenue increase from the year before entry to the year of entry. We applied this increase to 1999 in the first scenario and to 2001 in the second scenario.

- To estimate revenue growth before generic entry in Scenario 2, from 1998 to 2000, we increased revenues at a decreasing rate so that the 12.4% rate of growth declined to 10.4% and then to 7.4% before reaching 4.0% in 2001.
- After generic entry, we applied the same rate of branded revenue decline in both scenarios—22.3% from the year of entry to the year after entry, 28.0% from the year after entry to 2 years after entry, and 22.1% (the average yearly decline for Megace from 5 to 8 years after generic entry) every year thereafter.

All trends in revenues for branded paclitaxel were taken from wholesaler revenue data for Megace, VePesid, Hydrea and Mutamycin (Table 3). Years after entry are not calendar years but consecutive 12-month periods in relation to what would have been October generic entry. For example, etoposide generic entry occurred in February 1994, but data for the brand VePesid were grouped so that the month of generic entry is in the tenth month (October) of the year of generic entry. This allowed us to look at trends assuming that all drugs faced generic competition in the same relative time period as Taxol.

We then estimated brand and generic market share in terms of revenues as a percentage of total market share from our data on the four BMS cancer drugs (Table 4). We applied the brand market share data to calculate total paclitaxel sales and then subtracted brand sales from total sales to estimate generic sales in Scenario 1. Finally, we used generic sales in Scenario 1, but

TABLE 3. Rate of Revenue Change of Four Branded Cancer Drugs in Relation to Generic Entry.

Brand	Year in Relation to Generic Entry									
	2 Years Before to 1 Year Before	Year Before to Year of Entry	Year of Entry to 1 Year After	1-2 Years After	2-3 Years After	3-4 Years After	4-5 Years After	5-6 Years After	6-7 Years After	7-8 Years After
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Megace	-	13.4%	□ 17.2% ¹	□ 22.1% ²	0.1% ³	10.2% ⁴	□ 8.9% ⁴	□ 30.6%	□ 13.1%	□ 22.6%
VePesid	31.8%	□ 7.9%	□ 23.4%	□ 33.9%	-	-	-	-	-	-
Hydrea	11.0%	12.6%	□ 23.5%	-	-	-	-	-	-	-
Mutamycin	□ 5.6%	□ 2.3%	□ 24.9%	-	-	-	-	-	-	-
Average	12.4%	4.0%	□ 22.3%	□ 28.0%	0.1%	10.2%	□ 8.9%	□ 30.6%	□ 13.1%	□ 22.6%
Average of Columns (9)-(11)	□ 22.1%									

- Data not available

Notes: ¹ Generic entry occurs in October.

² Represents the average of columns (5)-(11). Actual data for this year are not used. See footnote 3.

³ Not used in model because rise in brand revenues represents a rise in overall usage of the drug due to increased usage for weight loss in AIDS patients.

⁴ Column (7) is overstated and column (8) is understated because of an addition of sales channels in IMS data collection.

Generic entry for megestrol acetate, etoposide, hydroxyurea, and mitomycin occurred in June 1993, February 1994, October 1995, and June 1995, respectively.

Source: Data on revenues for megestrol acetate, etoposide, hydroxyurea, and mitomycin from October 1988 to December 1996, IMS America, IMS Corporation.

TABLE 4. Market Share by Revenue of Four Cancer Drugs—Brand and Generic Competitors—from Year of Generic Entry to 8 Years After Generic Entry.

Producer	Year of Generic Entry	Years after Generic Entry							
		1	2	3	4	5	6	7	8
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Megestrol Acetate									
BMS (Megace)	100.0%	96.3%	89.3%	72.0%	64.7%	57.5%	44.0%	36.8%	32.8%
Par Pharm	-	-	-	-	8.8%	14.2%	21.9%	25.0%	25.8%
Glaxo	-	-	-	-	7.1%	6.3%	8.8%	8.1%	8.1%
Rugby	-	3.7%	9.7%	11.9%	8.2%	7.3%	8.2%	7.2%	7.3%
RKG	-	-	-	-	-	0.8%	2.4%	2.3%	2.5%
Schein	-	-	-	-	-	0.7%	2.8%	4.0%	4.8%
Qualitest	-	-	-	-	1.3%	2.4%	3.0%	3.1%	3.2%
Lemmon	-	-	-	-	-	0.4%	1.4%	2.8%	2.9%
WAS	-	-	-	-	1.8%	1.1%	1.3%	1.5%	1.3%
Parmed	-	-	-	-	2.1%	2.2%	1.5%	1.8%	1.6%
PRL	-	-	-	-	0.9%	2.7%	3.0%	2.8%	1.8%
Major	-	-	-	-	1.2%	1.2%	0.8%	0.5%	1.0%
UNR	-	-	-	-	1.6%	1.2%	1.1%	0.9%	0.8%
Marlex	-	-	-	-	0.1%	0.3%	0.6%	0.6%	0.7%
Balan J.J.	-	-	-	-	0.2%	0.6%	0.8%	0.9%	0.8%
Pharmaceutical Basic	-	-	-	-	1.2%	1.0%	0.1%	0.1%	0.1%
Genelco	-	-	-	-	-	0.1%	0.0%	0.0%	0.0%
Aligen	-	-	-	-	-	-	-	1.7%	0.9%
Other *	-	-	1.0%	16.1%	0.7%	0.0%	0.6%	0.0%	4.0%
Total Generic Megestrol	0.0%	3.7%	10.7%	28.0%	35.3%	42.5%	56.0%	63.2%	67.2%
Etoposide									
BMS (Vepesid)	90.1%	87.4%	85.3%						
USA	0.9%	12.6%	9.4%						
(PRL) Toposar	-	-	5.3%						
(BMS) Etopophos	-	-	-						
Total Generic Etoposide	9.9%	12.6%	14.7%						
Hydroxyurea									
BMS (Hydrea)	97.9%	75.2%							
Generic Hydroxyurea**	2.1%	24.8%							
Mitomycin									
BMS (Mitomycin)	99.7%	96.4%							
Chiron	-	0.2%							
FDG	-	0.1%							
CYT	0.3%	3.4%							
Total Generic Mitomycin	0.3%	3.6%							
Simple Average of Branded Share	96.9%	84.8%	87.3%	72.0%	64.7%	57.5%	44.0%	36.8%	32.8%
Simple Average of Generic Share	3.1%	11.2%	12.7%	28.0%	35.3%	42.5%	56.0%	63.2%	67.2%

* Includes part-year sales by companies already listed in the table.

** Includes only one distributor, Roxane.

- Company does not sell the generic drug for the full 12 months.

Source: Data on revenues for megestrol acetate, etoposide, hydroxyurea and mitomycin from October 1986 to December 1996, IMS America, IMS Corporation.

built in a two-year delay to represent generic sales in Scenario 2. We merely delayed the revenue from sales of the generic products two years in Scenario 2. Alternatively, generic revenues in Scenario 2 could be higher than corresponding generic revenues in Scenario 1, as would be the case if we used the same relative market share estimates applied to higher revenue estimates. In fact, if anything, generic revenues in Scenario 2 should be lower than generic revenues in Scenario 1 for the reasons discussed above. However, we chose to use the same generic revenues in both scenarios. This most likely understates the costs.

To discount savings to a present value in 1997, we used a 7% discount rate, which is slightly higher than the current 10-year Treasury Bill rate of 6.60% (25). Since we are measuring savings to the health care system, we used an opportunity cost of the money to individuals or, in the case of Medicare and Medicaid, to the government. In either case, the risk can be represented by the opportunity foregone from not investing the money at 7%.

Using these assumptions, we estimate that the present value of the costs to the health care system from extending marketing exclusivity for Taxol for 2 years are \$1.09 billion. Table 5 and Figure 1 are numerical and graphical representations of our results, respectively.

Intermediary Margin

As discussed above, the margins taken by intermediaries on brand and generic products often differ. On average, generic products have a higher margin compared to the brand products. We determined that the intermediary margin for the brand products is 22.6% of the retail price, while the margin for generic products is 45.5%. Using these values in our market, the present value of the costs to the health care system from extending exclusivity for Taxol is \$1.27 billion (Table 6, Figure 2).

Costs to Medicare

Presently, Medicare reimburses at AWP for Taxol, while Medicaid programs receive a discount for prescription drug purchases including Taxol. In 1994, the Medicaid rebate on Taxol was equivalent to a 13% discount off AWP (26). In 1996, Medicare spent \$105.9 million for Taxol²⁶ out of total Taxol sales of \$762 million (if all sales had been at AWP). Approximately 13.9% of Taxol sales in 1996 were through Medicare.

TABLE 5. Costs Due to Extending Exclusivity for Taxol 1994-2005.

	With Total Marketing Exclusivity Expiring December 1997									
	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
(1) Projected BMS U.S. and MAX Sales (Sales + (Sales*(2)/(100)))	\$ 260	\$ 400	\$ 590	\$ 700	\$ 787	\$ 816	\$ 836	\$ 458	\$ 567	\$ 278
(2) Projected Revenue Increase	-	-	-	-	12.4%	4.7%	22.3%	28.0%	22.1%	22.1%
(3) Projected Generic Sales [(1)-(2)]	-	-	-	-	-	\$ 26	\$ 60	\$ 67	\$ 138	\$ 152
(4) Projected Total Pictorial Sales [(1)+(3)/(100)]	\$ 260	\$ 400	\$ 590	\$ 700	\$ 787	\$ 844	\$ 716	\$ 524	\$ 495	\$ 429
(5) Projected Generic Revenue Market Share	-	-	-	-	-	31%	11.2%	12.7%	28.0%	33.3%
(6) Projected BMS U.S. and MAX Sales (Sales + (Sales*(7)/(100)))	\$ 260	\$ 400	\$ 590	\$ 700	\$ 787	\$ 869	\$ 933	\$ 970	\$ 754	\$ 543
(7) Projected Revenue Increase	-	-	-	-	12.4%	10.4%	7.4%	4.0%	22.2%	28.0%
(8) Projected Generic Sales *	-	-	-	-	-	-	\$ 26	\$ 26	\$ 80	\$ 67
(9) Projected Total Pictorial Sales [(6)+(8)]	\$ 260	\$ 400	\$ 590	\$ 700	\$ 787	\$ 895	\$ 959	\$ 996	\$ 834	\$ 609
(10) Projected Savings in Pictorial Sales [(9)-(5)]	\$ 0	\$ 0	\$ 0	\$ 0	\$ 0	\$ 25	\$ 217	\$ 472	\$ 339	\$ 180
(11) Discount Rate **	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%
(12) PV of Savings Discounted to 1997 [(10)/(1+(100)/(100))^(year-1997)]	\$ 0	\$ 0	\$ 0	\$ 0	\$ 0	\$ 21	\$ 177	\$ 380	\$ 242	\$ 115
Total										\$ 1,082 million

* Represents years without generic competition.
 * Generic pictorial sales with exclusivity ending in 1999 below the exact same revenue trend except with a two-year delay as with 1997 exclusivity expiration.
 - Discount rate used is slightly higher than the 10-year T-bill rate of 6.62%.
 Source: Rows (1) and (6): 1994 from IMS data; 1995 from Smith Barney, October 23, 1996; 1996 from "British-Meyers Sizable Company (BMS)", Alex Brown, November 13, 1996, p. 5, and 1997 from "Pharma Pipeline: New Product Timelines for the Pharmaceutical Industry," Lehman Brothers, January 1998, p. B38.
 Rows (2) and (7): NEPA table: "Time of Revenue Change of Four Branded Cancer Drugs in Relation to Generic Entry."
 Row (5): NEPA table: "Market Share by Revenue of Four Cancer Drugs: Brand and Generic Competition."

We calculated the costs to Medicare from extending exclusivity for Taxol in a manner similar to that described above, with the following modifications:

- We began with BMS sales of Taxol evaluated at AWP (Table 6).
- Next, we recalculated generic sales in dollar terms as if they had been at the brand price, in effect converting brand and generic sales to units at brand AWP. Then we added brand and generic sales (at brand price) to obtain total paclitaxel sales at the brand AWP price.
- We applied our estimate of Medicare share of unit sales²⁷ to calculate Medicare's spending on paclitaxel. For the years before generic entry, the calculation was a simple percentage of total sales. For the years after generic entry, we took Medicare's share of unit sales and then multiplied the resulting number by 86%²⁸ to determine sales at the generic AWP price. Medicare reimburses at the median generic AWP for multi-source drugs (26). For the year of generic entry, we attributed 83% (ten-twelfths of a year) of sales to the brand price and 17% (two-twelfths of a year) of sales to the generic price.

FIGURE 1. Paclitaxel Sales Forecasts with Exclusivity Expiring in 1997 or 1999.

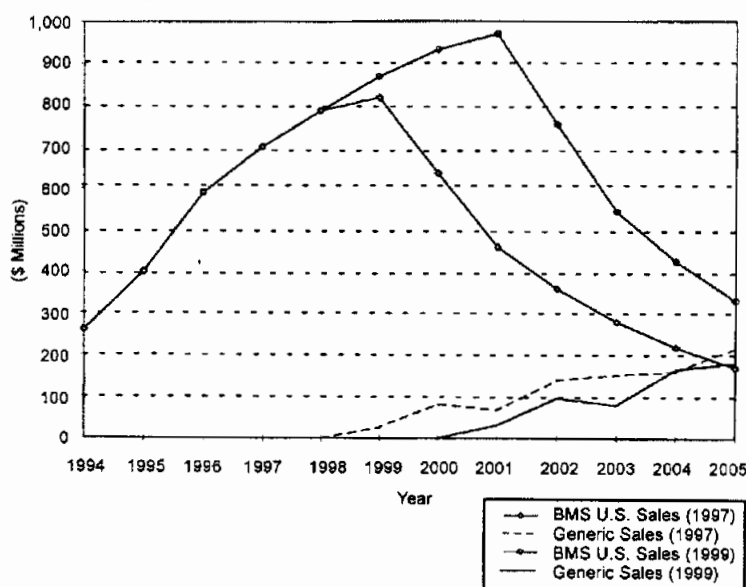


TABLE 6. Costs Due to Extending Exclusivity for Taxol Including an Intermediary Markup with Sales at AWP 1994-2005.

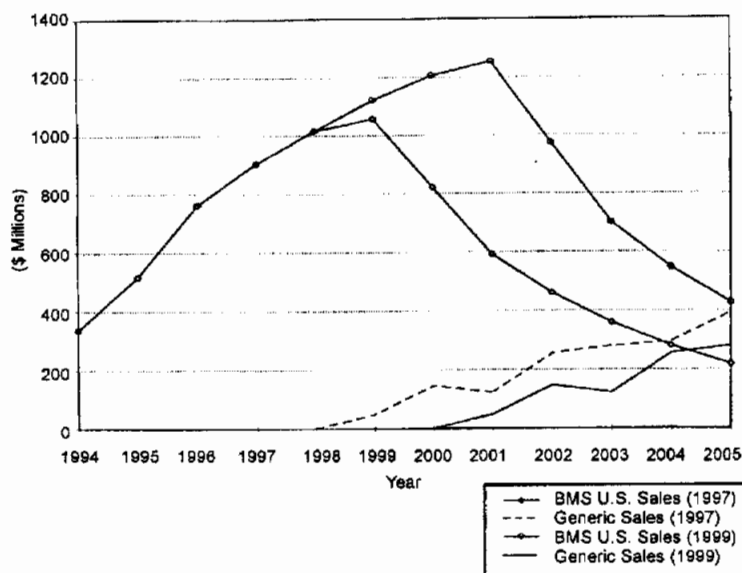
	With Taxol Marketing Exclusivity Expiring December 1997											
	1994	1995	1996	1997	1998	(\$ in Millions)						
						1999	2000	2001	2002	2003	2004	2005
(1) Projected BMS U.S. and IVAX Sales	\$ 260	\$ 400	\$ 590	\$ 700	\$ 787	\$ 813	\$ 836	\$ 838	\$ 357	\$ 278	\$ 216	\$ 189
(2) Projected Brand Sales at AWP	\$ 336	\$ 517	\$ 762	\$ 904	\$ 1017	\$ 1057	\$ 821	\$ 591	\$ 461	\$ 369	\$ 280	\$ 218
(3) Projected Generic Sales	-	-	-	-	-	\$ 26	\$ 80	\$ 67	\$ 139	\$ 152	\$ 160	\$ 215
(4) Projected Generic Sales at AWP	-	-	-	-	-	\$ 48	\$ 147	\$ 123	\$ 255	\$ 279	\$ 294	\$ 394
(5) Total Projected Preclinical Sales at AWP	\$ 336	\$ 517	\$ 762	\$ 904	\$ 1017	\$ 1105	\$ 968	\$ 714	\$ 716	\$ 638	\$ 573	\$ 612
(6) Projected BMS U.S. and IVAX Sales	\$ 260	\$ 400	\$ 590	\$ 700	\$ 787	\$ 869	\$ 933	\$ 970	\$ 754	\$ 643	\$ 423	\$ 329
(7) Projected Brand Sales at AWP	\$ 336	\$ 517	\$ 762	\$ 904	\$ 1017	\$ 1122	\$ 1205	\$ 1254	\$ 974	\$ 701	\$ 546	\$ 405
(8) Projected Generic Sales	-	-	-	-	-	-	\$ 26	\$ 26	\$ 80	\$ 67	\$ 139	\$ 152
(9) Projected Generic Sales at AWP	-	-	-	-	-	-	-	\$ 48	\$ 147	\$ 123	\$ 255	\$ 278
(10) Total Projected Preclinical Sales	\$ 336	\$ 517	\$ 762	\$ 904	\$ 1017	\$ 1122	\$ 1205	\$ 1301	\$ 1121	\$ 854	\$ 601	\$ 704
Costs Due to Exclusivity Expiring December 1999												
	1994	1995	1996	1997	1998	(\$ in Millions)						
						1999	2000	2001	2002	2003	2004	2005
(11) Projected Savings in Preclinical Sales	\$ 0	\$ 0	\$ 0	\$ 0	\$ 0	\$ 17	\$ 237	\$ 567	\$ 465	\$ 186	\$ 228	\$ 92
(12) Discount Rate (%)	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%
(13) PV of Savings	\$ 0	\$ 0	\$ 0	\$ 0	\$ 0	\$ 15	\$ 193	\$ 448	\$ 269	\$ 124	\$ 142	\$ 54
Total												
Total												

Note: Intermediary markup for branded products is 22.0% of retail price and 46.5% for generic products.
Source: NEHA tables. "Costs Due to Extending Exclusivity for Taxol" and "Intermediary Markup on Branded and Generic Versions of Four Cancer Drugs."

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FIGURE 2. Paclitaxel Sales Forecasts with Exclusivity Expiring in 1997 or 1999 Including an Intermediary Markup to AWP.



We repeated the above procedures for Scenario 2 and then subtracted Medicare payments in Scenario 1 from those in Scenario 2. Using a 7% discount rate, the present value of the costs to the Medicare program over the next 8 years of extending the exclusivity for Taxol are \$288 million (Table 7).

CONCLUSIONS

Based on our model, the present value of the costs to the health care system are approximately \$1.09 billion and \$1.27 billion at the seller and payer levels, respectively. That is, delaying competition for 2 years by extending BMS's marketing exclusivity for Taxol will cost consumers/insurers/government over \$1 billion. The added costs are \$288 million to Medicare alone.

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TABLE 7. Costs to Medicare from Extending Exclusivity for Taxol 1994-2005.

	With Taxol Marketing Exclusivity Expiring December 1997											
	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
	(\$ in Millions)											
(1) Projected BMS U.S. and MAX Sales at AMP	\$ 336	\$ 517	\$ 782	\$ 904	\$ 1017	\$ 1057	\$ 821	\$ 591	\$ 461	\$ 358	\$ 260	\$ 216
(2) Projected Generic Sales at AMP	-	-	-	-	-	\$ 48	\$ 147	\$ 173	\$ 255	\$ 279	\$ 254	\$ 304
(3) Generic Sales at AMP Brand Price [(2)/(1) x 100]	-	-	-	-	-	5%	17.1%	14.3%	29.7%	32.4%	34.2%	45.8%
(4) Total Projected Facilitated Sales	\$ 336	\$ 517	\$ 782	\$ 904	\$ 1017	\$ 1113	\$ 968	\$ 764	\$ 716	\$ 637	\$ 514	\$ 520
(5) Projected Medicare Share * [(4) x (5)]	8.3%	12.3%	13.9%	15.5%	17.1%	18.7%	20.3%	21.9%	23.5%	25.1%	26.7%	28.3%
(6) Projected Medicare Payments [(4) x (5) x (6)]	\$ 28	\$ 63	\$ 108	\$ 140	\$ 174	\$ 195	\$ 173	\$ 138	\$ 153	\$ 148	\$ 143	\$ 165
	With Taxol Marketing Exclusivity Expiring December 1999											
	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
	(\$ in Millions)											
(7) Projected BMS U.S. and MAX Sales at AMP	\$ 336	\$ 517	\$ 782	\$ 904	\$ 1017	\$ 1122	\$ 1205	\$ 1254	\$ 974	\$ 701	\$ 546	\$ 430
(8) Projected Generic Sales at AMP	-	-	-	-	-	-	-	\$ 48	\$ 147	\$ 123	\$ 255	\$ 279
(9) Generic Sales at AMP Brand Price [(8)/(7) x 100]	-	-	-	-	-	-	-	5%	17.1%	14.3%	29.7%	32.4%
(10) Total Projected Facilitated Sales	\$ 336	\$ 517	\$ 782	\$ 904	\$ 1017	\$ 1122	\$ 1205	\$ 1310	\$ 1145	\$ 844	\$ 643	\$ 750
(11) Projected Medicare Share * [(10) x (5)]	8.3%	12.3%	13.9%	15.5%	17.1%	18.7%	20.3%	21.9%	23.5%	25.1%	26.7%	28.3%
(12) Projected Medicare Payments [(10) x (5) x (11)]	\$ 28	\$ 63	\$ 108	\$ 140	\$ 174	\$ 210	\$ 245	\$ 230	\$ 231	\$ 182	\$ 183	\$ 183
	Costs from Exclusivity Expiring in 1999											
	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
	(\$ in Millions)											
(13) Projected Savings in Particular Sales	\$ 0	\$ 0	\$ 0	\$ 0	\$ 0	\$ 44	\$ 71	\$ 91	\$ 78	\$ 35	\$ 51	\$ 18
(14) Discount Rate ***	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%
(15) PV of Savings Discounted to 1997 [(13)/(1 - (14)/(100)) ^{Year 1997}]	\$ 0	\$ 0	\$ 0	\$ 0	\$ 0	\$ 39	\$ 58	\$ 70	\$ 56	\$ 23	\$ 32	\$ 11

\$238 million

* Represents years without generic competition.

** Medicare's share of particular sales increases 1.0 percentage points a year, which is the change in Medicare's percent share between 1995 and 1996.

*** In the year the generic enters, Medicare pays 65% branded and 17% generic. Formula for cost (5) in the year generic enters is: $[(5)/(5/(100) + 17) + (17)/(5/(100) + 17)] \times [17] \times (5)/(100)$.

For years 2000-2005, the formula is: $[(5)/(5/(100) + 17) + (17)/(5/(100) + 17)] \times [17] \times (5)/(100)$.

For the year the generic enters, Medicare pays 65% branded and 17% generic. Formula for cost (5) in the year generic enters is: $[(5)/(5/(100) + 17) + (17)/(5/(100) + 17)] \times [17] \times (5)/(100)$.

For years 2000-2005, the formula is: $[(5)/(5/(100) + 17) + (17)/(5/(100) + 17)] \times [17] \times (5)/(100)$.

*** Discount rate used in step 14 is higher than the 10-year T-bill rate of 6.00%.

Source: NETA table: Costs Due to Extending Exclusivity for Taxol including an immediate Mark-up with Sales at AMP and from Karen Boehle, Health Care Financing Administration, to Ruth Berkowitz dated March 10, 1997.

NOTES

1. The U.S. Food and Drug Administration (FDA) approved Taxol for refractory ovarian cancer on December 29, 1992, and for refractory breast cancer on April 12, 1994. In addition, Taxol is used off-label for other types of cancer. Presently, clinical trials are under way with paclitaxel for the treatment of a variety of problems including non-small-cell lung cancer, head and neck cancer, brain tumors, solid tumors, Kaposi's sarcoma, melanoma, lymphoma, pancreatic cancer, esophageal cancer, and germ cell neoplasms. Taxol is generally reimbursed by insurers for use in cancer treatment.

2. Under the extended CRADA, BMS also received worldwide rights to certain other anticancer technologies developed by NCI (4).

3. Proposed legislation would grant extended marketing exclusivity to certain drugs, including Taxol, in exchange for 3% royalties to the NIH (5).

4. We did not include doxorubicin (Rubex[®]) in our study because we understand BMS was not the innovator of this product and generic versions of the product are available in a liquid, as opposed to powder, formulation. The liquid form may be easier to use and, thus, the generic firms may have a larger market share due to this factor. We did not want to overstate the impact of generic entry.

5. Other off-label uses include choriocarcinoma, Ewing's sarcoma, Kaposi's sarcoma in patients with AIDS, neuroblastoma, rhabdomyosarcoma, and hydatiform moles (6).

6. Off-label uses include sickle cell anemia, hypereosinophilic syndrome, recalcitrant psoriasis, and chronic urinary tract infections (6).

7. Megace oral suspension is indicated for anorexia, cachexia, or weight loss in patients with AIDS. For the purpose of our analysis, we exclude sales of Megace oral suspension from our data.

8. Megestrol acetate is also used off-label to reduce levels of gonadotropins and the secretion of testosterone in benign prostatic hypertrophy, to relieve symptoms of endometriosis, for symptomatic stage D prostatic cancer, and as a contraceptive (6).

9. BMS has already announced a private label version of Taxol prior to expiration of exclusivity (7).

10. BMS could license the rights to its NDA for Taxol to its generic subsidiary, Apothecon, prior to its exclusivity expiring. Apothecon would not need to obtain a separate approval from the FDA.

11. Given that FDA approval of a generic product means that it is bioequivalent to the reference drug, this is a matter of perception rather than reality.

12. Paxene is the IVAX brand of paclitaxel.

13. ChiRex will manufacture paclitaxel at its U.K. facility. Under a contract with the Nepalese government, part of the InNova joint venture, Dabur, has exclusive rights to harvest the first 800 metric tons of Himalayan yew needles per year (12).

14. AWP does not reflect discounts offered by BMS; that is, AWP does not necessarily provide the price at which transactions take place.

15. Since the mid-1990s, BMS has lowered the manufacturer price of its other oncology products facing generic competition. The manufacturer price of Megace, Hydrea, and Mutamycin has decreased annually since 1994, and the manufacturer price of VePesid has decreased annually since 1993 (Table 2). Moreover, Grabowski

and Vernon found that for injectables, "the more prevalent pattern is for the incumbent firm to cut prices in the face of generic competition, although not to the lowest level of the generic entrants" (13).

16. "Pricing—The price of generic products is a direct function of the number of generic manufacturers that receive approval . . . Unit penetration—The more competitors, the greater the penetration" (17).

17. The definition of a blockbuster drug used here is one that has more than \$50 million in annual sales.

18. Other prospects for generic firms appear by 2000. Drugs with patent expiring in 2000 and 2001 include Vasotec[®], Prozac[®], Prilosec[®], and Pepcid[®] (18).

19. There are a number of examples where two brands of the same chemical have similar AWP's, such as Proventil[®] and Ventolin[®], Fortaz[®] and Tazidime[®], and Prinivil[®] and Zestril[®].

20. A GAO report estimated retail oncology drug costs to be 170% of wholesale drug costs (22).

21. Since AWP overstates actual price, but may overstate it by differing margins for branded and generic drugs, our calculation of savings with a markup is not an upper bound to savings.

22. The "GAO found that off-label use of anticancer drugs is widespread" (22).

23. Given the focus on cost containment in health care and that hospitals and physicians are knowledgeable about the bioequivalence of brand and generic versions of products, price competition will emerge once the generics are available.

24. Costs may extend further into the future.

25. Alex. Brown estimates \$710 million for 1997 (23).

26. The current data available indicate spending of \$90,022,882 for Taxol. According to Ms. Beebe, these data represent 85% of total spending for 1996 (27).

27. We projected Medicare's share of paclitaxel sales to increase at 1.6% a year, which is the change in Medicare's percentage share between 1995 and 1996.

28. We calculated the price of our sample of generic cancer drugs to be 86% of the price of their brand competitors at AWP (Table 6).

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